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(54) **COMPRESSED TABLETS**

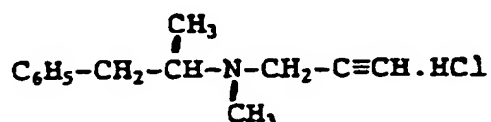
(57) Direct compression tablets were produced by dry blending a pharmaceutical active ingredient, preferably selegiline, oxybutynin, indapamide or bumetanide, an excipient and an inhibitor to reduce or prevent the interaction between the active agent and excipient. The inhibitor is preferably a starch based or cellulose based product, such as maize starch, or a crospovidone product. Lubricants and antioxidants may also be included.

GB 2 295 966 A

"Pharmaceutical Tablet Formulations"

The invention relates to a pharmaceutical tablet formulation of an active pharmaceutical ingredient and to a method for producing such tablets.

5 UK-A-1,153,578 describes selegiline hydrochloride which is the compound of the formula



10 It has 5 monoamine oxidase inhibitor activity and is used in the treatment of Parkinsons disease and as a coronary dilator, hallucinogenic and anti-depressive agent and also as a tranquilliser, analgesic and an appetite suppressant.

15 It is known to formulate selegiline in tablet form using conventional wet granulation techniques. However, to date it has not been possible to produce a satisfactory tablet composition of selegiline by direct compression techniques. Similar problems have arisen with other active pharmaceutical ingredients.

20 Direct compression is the preferred technique since it is considered that fewer chemical stability problems are associated with this technique in comparison with the wet granulation process as moisture is considered to be a primary cause of instability in tablet dosage forms. In
25 addition to the advantage of improved active ingredient stability, the use of direct compression makes it unnecessary to use applied heat to dry the damp granule. Other benefits associated with direct compression are related to particle size uniformity.

This invention therefore is directed towards a direct compression pharmaceutical tablet formulation of an active pharmaceutical ingredient.

5 According to the invention, there is provided a direct compression pharmaceutical tablet formulation comprising:

an active pharmaceutical ingredient,

a direct compression excipient which interacts with the active pharmaceutical ingredient, and

10 an amount of an inhibitor to reduce the interaction between the direct compression excipient and the active pharmaceutical ingredient.

15 In a preferred embodiment of the invention the formulation contains an amount of the inhibitor to substantially prevent the interaction between the direct compression excipient and the active pharmaceutical ingredient.

20 In one preferred embodiment of the invention the weight ratio of inhibitor to the active pharmaceutical ingredient is from 1:50 to 4:1, ideally from 8:5 to 12:5. Preferably the inhibitor includes a starch, starch-derived or cellulose-derived product, especially maize starch.

In another embodiment of the invention, the inhibitor includes a crospovidone based product.

25 In a preferred embodiment of the invention the excipient is direct compression lactose and/or microcrystalline cellulose.

The weight ratio of direct compression lactose to active pharmaceutical ingredient is preferably from 2:1 to 100:1 most preferably from 7:1 to 50:1, ideally from 8:1 to 11:1.

- 5 The weight ratio of microcrystalline cellulose to active pharmaceutical ingredient is preferably from 2:1 to 100:1, most preferably from 3:1 to 17:1, ideally from 4:1 to 16:1.

10 In one embodiment of the invention, the formulation includes a lubricant, preferably from 0.1% to 5%, most preferably approximately 0.25% by weight of the formulation. The lubricant may be magnesium stearate, zinc stearate, calcium stearate, stearic acid or combinations of these materials.

15 In one embodiment of the invention, the formulation includes an antioxidant or other suitable stabiliser to enhance the stability of the tablet formulation. Preferably the antioxidant is present in an amount of from 0.5% to 2% by weight of the formulation.

20 In another embodiment of the invention the formulation may include glidants, disintegrants, fillers, wetting agents, stabilisers, binders, or combinations of these materials.

25 The active pharmaceutical ingredient may be selegiline or a pharmaceutically acceptable salt thereof, preferably selegiline hydrochloride. The active pharmaceutical ingredient may also be other compounds including oxybutynin or a pharmaceutically acceptable salt thereof, preferably oxybutynin chloride; bumetanide or a pharmaceutically acceptable salt thereof; or indapamide or
30 a pharmaceutically acceptable salt thereof, preferably indapamide hemihydrate.

The invention also provides a method of preparing a tablet by preparing a formulation according to the invention and directly compressing said formulation to form a tablet.

5 The invention further provides a method for producing tablets of an active pharmaceutical ingredient comprising the steps of:-

10 mixing the active pharmaceutical ingredient, a lubricant, a direct compression excipient, and an amount of an inhibitor to substantially prevent interaction between the direct compression lactose and the active pharmaceutical ingredient; and

directly compressing the mixture thus formed to form tablets.

15 Preferably the formulation includes a lubricant and the method includes the step of mixing the ingredients except the lubricant and subsequently adding the lubricant. Preferably the mixing is a dry blending technique. The excipient is preferably direct compression lactose.

20 The inhibitor preferably includes a starch, starch-derived or cellulose-derived product. Alternatively, the inhibitor includes a crospovidone based product.

The invention will be more clearly understood from the following description thereof given by way of example only.

25 In each case, the formulation is a direct compression formulation. The ingredients were weighed out and all the ingredients except the lubricant were added to a receptacle and dry blended for about 6 minutes. The

lubricant (in these cases magnesium stearate) was then added and the mixture is blended for a further 2 minutes. Tablets were then formed from the blend by conventional direct compression techniques.

- 5 In Examples A and 1 to 4, selegiline hydrochloride was used as the active ingredient. However, it will be appreciated that selegiline base or any pharmaceutically acceptable salt thereof may be used as the active ingredient. Similar comments apply to the examples referring to other active ingredients. In examples B and 10 5 oxybutynin chloride was used. In example 9 indapamide hemihydrate was used.

All of the excipients used in the examples are of pharmaceutical grade.

- 15 Magnesium Stearate: consists mainly of magnesium stearate with variable proportions of magnesium palmitate and/or magnesium oleate. It is a tablet lubricant. 20

- Zinc Stearate: consists mainly of zinc stearate with variable proportions of zinc palmitate and zinc oleate. It is a tablet lubricant. 25

- Sodium Lauryl Sulfate: an anionic surfactant used as a detergent and wetting agent in tablet formulations.

Croscarmellose Sodium: is a cross-linked polymer of carboxymethylcellulose sodium. It is a tablet disintegrant.

5 Sodium Starch Glycolate: is the sodium salt of a poly- α -glucopyranose in which some of the hydroxyl groups are in the form of carboxymethyl ether. It is a tablet disintegrant.

10 Crospovidone: is a water insoluble synthetic cross-linked homopolymer of N-vinyl-2-pyrrolidone. It is a tablet disintegrant.

15 Microcrystalline Cellulose: is a purified, partially depolymerised cellulose and is used as a diluent and has some lubricant and disintegrant properties.

20 Direct Compression Lactose (DC Lactose): is direct compression grade of lactose which is more fluid and more compressible than crystalline or powdered lactose.

25 Various proprietary brands of direct compression lactose are commercially available. In the examples given below, the brand of direct compression lactose used was Tablettose 80 available from Meggle GmbH of Germany. We have also achieved similar results using Pharmatose DC11 which is available from DMV International of The
30 Netherlands.

It will be appreciated that various similar formulations to those described below may be prepared by scaling up or down the components of the mixture so that the new formulation is quantitatively proportional to those given below. For example, formulations containing 10 mgs of selegiline may be prepared in this way. Similarly, an oxybutynin formulation may be prepared in this way with 2.5 mg rather than 5 mg of active. In addition, a bumetanide formulation may also be prepared in this way with 1 mg rather than 5 mg of active ingredient.

EXAMPLE A

A batch of tablets were prepared by direct compression.
Each tablet had the following composition:-

5	5 mg	selegiline hydrochloride
	85 mg	DC Lactose

The tablets gave an assay of 91.8%.

This example illustrates the low assay that results when tablets of selegiline are manufactured by direct compression techniques using direct compression lactose.

10 EXAMPLE 1

A batch of tablets were prepared by direct compression.
Each tablet had the following composition:-

	5 mg	selegiline hydrochloride
	52.75 mg	DC Lactose
15	24 mg	microcrystalline cellulose
	8 mg	maize starch
	0.25 mg	magnesium stearate

The tablets gave an assay of 99.5%.

20 It will be noted that the use of an inhibitor, in this case maize starch, radically improves the assay result.

EXAMPLE 2

A batch of tablets were prepared by direct compression.
Each tablet had the following composition:-

	5 mg	selegiline hydrochloride
5	48.75 mg	DC Lactose
	24 mg	microcrystalline cellulose
	12 mg	maize starch
	0.25 mg	magnesium stearate

The tablets gave an assay of 97.94%.

- 10 Using a larger amount of maize starch and less DC Lactose did not significantly effect the assay.

EXAMPLE 3

A batch of tablets were prepared by direct compression.
Each tablet had the following composition:-

15	5 mg	selegiline hydrochloride
	48.75 mg	DC Lactose
	24 mg	microcrystalline cellulose
	11 mg	maize starch
	1 mg	citric acid
20	0.25 mg	magnesium stearate

The tablets gave an assay of 99.6%.

The addition of an antioxidant, in this case citric acid, is to counteract any oxidation reactions in storage.

EXAMPLE 4

A batch of tablets were prepared by direct compression. Each tablet had the following composition:-

	5 mg	selegiline hydrochloride
5	49.45 mg	Direct Compression Lactose
	24 mg	Microcrystalline Cellulose
	11 mg	Maize Starch
	0.55 mg	Zinc Stearate

The tablets gave an assay of 100.7%

- 10 From extensive research and development in producing tablets of selegiline by direct compression techniques, we have noticed a very significant interaction between selegiline hydrochloride and conventional bulking agents such as DC Lactose and microcrystalline cellulose. It has
- 15 not been possible using conventional formulations to produce a tablet of selegiline by direct compression without a very significant adverse affect on the assay results for the tablets produced. In all cases, the assay was found to be less than 95%, in some cases, as low as
- 20 70%. It is not fully understood why such poor assay results were obtained. It is, however, speculated that there may be an interaction between the selegiline and the DC Lactose and microcrystalline cellulose, resulting possibly in the formation of a complex which adversely
- 25 affects the amount of selegiline detectable or available on assay. We have surprisingly found that the interaction is avoided and good assay results are obtained if an inhibitor, particularly maize starch, is incorporated especially in the amounts mentioned above.
- 30 It will be appreciated that it may be possible to use direct compression excipients either in addition to or as

an alternative either to direct compression lactose or microcrystalline cellulose. Such direct compression excipients include calcium hydrogen phosphate, compressible sugar, dextrates, and pregelatinized starch.

- 5 It will be appreciated that the formulation may include any suitable lubricant such as magnesium stearate or zinc stearate as described above or other stearic acid salts such as calcium stearate. Other suitable lubricants may also be incorporated, including glyceryl monostearate,
- 10 glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil type 1, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulphate, sodium stearyl fumarate, stearic acid and talc.
- 15 It will also be appreciated that while the presence of an antioxidant may not be essential, in cases where such an antioxidant is used it may be selected from one or more of the following: alpha tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated
- 20 hydroxytoluene, citric acid, fumaric acid, malic acid, propylgallate, sodium ascorbate, sodium metabisulphite.

We have also found that the interactions described above also apply to other active pharmaceutical ingredients. The following examples illustrate how similar techniques

25 may also be applied to direct compression pharmaceutical tablet formulations of active ingredients other than selegiline.

EXAMPLE B - COMPARISON

A batch of tablets were prepared by direct compression.
Each tablet had the following composition:-

	5 mg	oxybutynin chloride
5	174 mg	DC Lactose
	1 mg	Magnesium Stearate

The tablets gave an assay of 88.3%.

EXAMPLE 5

10 A batch of tablets were prepared by direct compression.
Each tablet had the following composition:-

	5 mg	oxybutynin chloride
	119 mg	DC Lactose
	43 mg	microcrystalline cellulose
	12 mg	crospovidone
15	1 mg	magnesium stearate

The tablets gave an assay of 97.9%.

EXAMPLE C - COMPARISON

A batch of tablets were prepared by direct compression.
Each tablet had the following composition.

5 5 mg bumetanide
 343 mg DC Lactose
 2 mg magnesium Stearate

The tablets gave an assay of 91%.

EXAMPLE D - COMPARISON

10 A batch of tablets were prepared by direct compression.
 Each tablet had the following composition.

 5 mg bumetanide
 343 mg microcrystalline cellulose
 2 mg magnesium stearate

The tablets gave a assay of 93.7%.

15 EXAMPLE 6

A batch of tablets were prepared by direct compression.
Each tablet had the following composition.

20 5 mg bumetanide
 237.5 mg DC Lactose
 80 mg microcrystalline cellulose
 25 mg crospovidone
 2.5 mg magnesium stearate

The tablets gave an assay of 97.4%.

EXAMPLE 7

A batch of tablets were prepared by direct compression.
Each tablet had the following composition.

	5 mg	bumetanide
5	237.5 mg	DC Lactose
	80 mg	microcrystalline cellulose
	25 mg	maize starch
	2.5 mg	magnesium stearate

The tablets gave an assay of 98.2%.

10 EXAMPLE 8

A batch of tablets were prepared by direct compression.
Each tablet had the following composition.

	5 mg	bumetanide
	241 mg	DC Lactose
15	80 mg	microcrystalline cellulose
	17 mg	croscarmellose sodium
	5 mg	sodium lauryl sulphate
	2 mg	magnesium stearate

The tablets gave an assay of 97.9%

20 EXAMPLE 9

A batch of tablets were prepared by direct compression.
Each tablet had the following composition:-

	2.5 mg	indapamide hemihydrate
	82.75 mg	DC Lactose
25	4 mg	carboxymethyl starch
	0.75 mg	magnesium stearate.

The tablets gave an assay of 100.4%.

It will be appreciated that similar techniques may be applied to produce direct compression tablet formulations of other active pharmaceutical ingredients which interact
5 with direct compression excipients.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

CLAIMS

1. A direct compression pharmaceutical tablet formulation comprising:

an active pharmaceutical ingredient,

5 a direct compression excipient which interacts with the active pharmaceutical ingredient,

and an amount of an inhibitor to reduce the interaction between the direct compression excipient and the active pharmaceutical ingredient.

10

2. A direct compression pharmaceutical tablet formulation as claimed in claim 1 wherein the formulation contains an amount of the inhibitor to substantially prevent the interaction between the direct compression excipient and the active pharmaceutical ingredient.
- 15

3. A formulation as claimed in claim 1 or 2 wherein the weight ratio of inhibitor to the active pharmaceutical ingredient is from 1:50 to 4:1.

- 20 4. A formulation as claimed in any of claims 1 to 3 wherein the weight ratio of inhibitor to the active pharmaceutical ingredient is from 8:5 to 12:5.

5. A formulation as claimed in any preceding claim wherein the inhibitor includes a starch, starch-derived or cellulose-derived product.
- 25

6. A formulation as claimed in any preceding claim wherein the inhibitor includes a maize starch.

7. A formulation as claimed in any proceeding claim in which the inhibitor includes a crospovidone based product.
- 5 8. A formulation as claimed in any preceding claim wherein the excipient includes direct compression lactose.
- 10 9. A formulation as claimed in claim 8 wherein the weight ratio of direct compression lactose to the active pharmaceutical ingredient is from 2:1 to 100:1.
- 10 10. A formulation as claimed in claim 8 or 9 wherein the weight ratio of direct compression lactose to the active pharmaceutical ingredient is from 7:1 to 50:1.
- 15 11. A formulation as claimed in any of claims 8 to 10 wherein the weight ratio of direct compression lactose to the active pharmaceutical ingredient is from 8:1 to 11:1.
- 20 12. A formulation as claimed in any preceding claim wherein the excipient includes microcrystalline cellulose.
13. A formulation as claimed in claim 12 wherein the weight ratio of microcrystalline cellulose to active pharmaceutical ingredient is from 2:1 to 100:1.
- 25 14. A formulation as claimed in claim 12 or 13 wherein the weight ratio of microcrystalline cellulose to active pharmaceutical ingredient is from 3:1 to 17:1.

15. A formulation as claimed in any of claims 12 to 14 wherein the weight ratio of microcrystalline cellulose to active pharmaceutical ingredient is from 4:1 to 16:1.
- 5 16. A formulation as claimed in any preceding claim including a lubricant.
17. A formulation as claimed in claim 16 wherein the lubricant is present in an amount from 0.1% to 5% by weight of the formulation.
- 10 18. A formulation as claimed in claim 17 wherein the lubricant is present in an amount of approximately 0.25% by weight of the formulation.
- 15 19. A formulation as claimed in any preceding claim including an antioxidant or other suitable stabiliser to enhance the stability of the tablet formulation.
- 20 20. A formulation as claimed in claim 19 wherein the antioxidant is present in an amount from 0.5% to 2% by weight of the formulation.
- 20 21. A formulation as claimed in any proceeding claim including either a glidant, a disintegrant, a filler, a wetting agent, stabiliser, a binder or any combination of these materials.
- 25 22. A formulation as claimed in any preceding claim wherein the active pharmaceutical ingredient is selegiline or a pharmaceutically acceptable salt thereof, preferably selegiline hydrochloride.
23. A formulation as claimed in any of claims 1 to 21 wherein the active pharmaceutical ingredient is

oxybutynin or a pharmaceutically acceptable salt thereof, preferably oxybutynin chloride.

24. A formulation as claimed in any of claims 1 to 21
5 wherein the active pharmaceutical ingredient is
bumetanide or a pharmaceutically acceptable salt
thereof.
25. A formulation as claimed in any of claims 1 to 21
10 wherein the active pharmaceutical ingredient is
indapamide or a pharmaceutically acceptable salt
thereof, preferably indapamide hemihydrate.
26. A direct compression pharmaceutical tablet
formulation substantially as hereinbefore described
with reference to examples 1 to 3.
27. A direct compression pharmaceutical tablet
15 formulation substantially as hereinbefore described
with reference to example 4.
28. A direct compression pharmaceutical tablet
formulation substantially as hereinbefore described
with reference to example 5.
- 20 29. A direct compression pharmaceutical tablet
formulation substantially as hereinbefore described
with reference to examples 6, 7 and 8.
30. A direct compression pharmaceutical tablet
25 formulation substantially as hereinbefore described
with reference to example 9.
31. A method of preparing a tablet comprising:

preparing a formulation as claimed in any preceding claim; and

directly compressing said formulation into a tablet.

- 5 32. A method for producing tablets of an active pharmaceutical ingredient comprising the steps of:-

10 mixing the active pharmaceutical ingredient, a lubricant, a direct compression excipient, and an amount of an inhibitor to reduce interaction between the direct compression excipient and the active pharmaceutical ingredient; and

 directly compressing the mixture thus formed to form tablets.

- 15 33. A method as claimed in claim 32 wherein the method includes the step of mixing the ingredients except the lubricant; subsequently adding the lubricant; and further mixing the ingredients.

34. A method as claimed in claim 32 or 33 wherein the mixing is performed using a dry blending technique.

- 20 35. A method as claimed in any of claims 32 to 34 wherein the direct compression excipient includes direct compression lactose.

- 25 36. A method as claimed in any of claims 32 to 35 wherein the inhibitor includes a starch, a starch-derived product, a cellulose-derived product or a derivative thereof.

37. A method as claimed in any of claims 32 to 36 wherein the inhibitor includes a crosopvidone based product.
38. A method as claimed in any of claims 31 to 37 wherein the active pharmaceutical ingredient is selegiline or a pharmaceutically acceptable salt thereof, preferably selegiline hydrochloride.
39. A method for producing tablets of an active pharmaceutical ingredient substantially as hereinbefore described with reference to examples 1 to 9.
40. A method for producing tablets of selegiline substantially as hereinbefore described with reference to examples 1 to 4.
41. A method for producing tablets of oxybutynin substantially as hereinbefore described with reference to example 5.
42. A method for producing tablets of bumetanide substantially as hereinbefore described with reference to examples 6, 7 and 8.
43. A method for producing tablets of indapamide substantially as hereinbefore described with reference to example 9.
44. Tablets of an active pharmaceutical ingredient whenever produced by a method as claimed in any of claims 31 to 43.
45. Tablets of selegiline or a pharmaceutically acceptable salt thereof, preferably selegiline

hydrochloride whenever produced by a method as claimed in any of claims 31 to 40.

5 46. Tablets of oxybutynin or a pharmaceutically acceptable salt thereof, preferably oxybutynin chloride whenever produced by a method as claimed in any of claims 31 to 39 or 41.

47. Tablets of bumetanide or a pharmaceutically acceptable salt thereof whenever produced by a method as claimed in any of claims 31 to 39 or 42.

10 48. Tablets of indapamide or a pharmaceutically acceptable salt thereof, preferably indapamide hemihydrate whenever produced by a method as claimed in any of claims 31 to 39 or 43.

15 49. A tablet prepared or preparable from a formulation as claimed in any of claims 1 to 30.



Application No: GB 9525598.0
Claims searched: 1-49

Examiner: JAMES HOULIHAN
Date of search: 19 March 1996

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK CI (Ed.O): A5B (BLM)

Int CI (Ed.6):

Other: ONLINE: CAS ONLINE, WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	GB 2207353 A (E.R SQUIBB & CO.) page 7 line 30-page 8 line 29; Example 8	1-4, 8, 12, 16, 21, 31-36, 49
P/X	EP 0628313 A1 (TAKEDA CHEM. IND.) page 10 lines 20-29, 41-49; Formulation examples 2,5,8, 11-13, 15 & 17	1-5, 8-11, 16, 17, 21, 24, 25, 31, 32, 35, 36, 49
X	EP 0519820 A1 (ADIR ET COMPAGNIE) page 2 lines 39-41; Examples 1-3	1, 2, 5, 8, 16, 21, 25, 31-33, 35, 36, 44, 48, 49
X	EP 0511767 A1 (MERCK & CO INC.) page 2 lines 35-38; Examples 1 & 2	1-3, 5, 8, 12, 16, 17, 21, 31-36, 49
P/X	WO 95/17169 A1 (APPLIED ANALYT. IND.) page 2 lines 16-22; Example 1	1, 2, 5, 12, 13, 16, 17, 21, 31-34, 36, 44, 49

X Document indicating lack of novelty or inventive step
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P Document published on or after the declared priority date but before the filing date of this invention.
E Patent document published on or after, but with priority date earlier than, the filing date of this application.



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Application No: GB 9525598.0
Claims searched: 1-49

Examiner: JAMES HOULIHAN
Date of search: 19 March 1996

Category	Identity of document and relevant passage	Relevant to claims
P/X	WO 94/28936 A1 (CIBA-GEIGY) page 10 lines 6-16; Examples 1-4	1-5, 12, 16, 17, 21, 31-34, 36, 49
X	WO 90/01928 A1 (CHINOIN GYOGYSZER) Example 2	1-3, 5, 8-11, 16, 17, 21, 22, 31-36, 38, 45, 49
X	US 5358717 (SYNTEX USA INC.) c.2 lines 25-38; Examples 1 & 3	1-3, 16, 17, 18, 19, 21, 31, 32, 36, 49
X	US 5057321 (ALZA CORP.) Example 6	1-5, 12, 16, 17, 19, 21, 22, 31, 3, 34, 36, 38, 45, 49
X	US 5047246 (BRISTOL MYERS CO.) c.2 lines 60-69; Examples 1-3	1-3, 5, 8, 12-14, 16, 17, 21, 31, 34, 36, 49
X	S.T.P. PHARM. SCI. VOL. 3 (6) 1993. SIRKIA T <i>et. al.</i> "Use of hydrophilic polymers to control drug release from press coated oxybutynin hydrochloride tablets" pages 453-458	1, 2, 8-11, 16, 17, 23, 31-33, 35, 41, 46, 49

X Document indicating lack of novelty or inventive step
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A Document indicating technological background and/or state of the art.
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